GGCCTG repeats put a hex on Purkinje cells and motor neurons in SCA36

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Editorial

An increasing number of neurologic disorders are caused by microsatellite, or simple sequence, repeat expansions. A group of diseases caused by polyglutamine-coding CAG expansions, including Kennedy disease, Huntington disease, and several spinocerebellar ataxias (SCAs), constitutes the prototype of such disorders. There is also a group of disorders caused by small expansions of polyalanine-coding GCN repeats, including oculopharyngeal muscular dystrophy. These disorders may result from the production of toxic proteins containing abnormally long tandem stretches of repeated amino acids. Researchers have also found that expanded microsatellite repeats located in noncoding regions are responsible for neurodegenerative disorders. The repeat motifs involved in these disorders include not only trinucleotide repeats but also tetranculeotide and pentanucleotide repeats. Pathogenic mechanisms of many of these disorders have been attributed to either altered transcription or a gain of a novel function of the RNA transcript of the respective genes. Furthermore, levels of microRNAs, highly conserved small RNA molecules consisting of ~21 nucleotides regulating expression of multiple target genes, are misregulated by repeat expansions. Additionally, the expanded complementary repeat sequence on the opposite strand may be transcribed at some of these disease loci. Finally, repeat associated non-AUG (RAN) translation of repeats in up to 3 frames from each of the 2 complementary transcripts may produce up to 6 different expanded amino acid repeats. Some or all of these repeat expansion products could contribute to pathogenic pathways in repeat expansion disorders. In the midst of these research advancements, 2 new disorders have been identified with an expansion of untranslated hexanucleotide repeats: a GGGGCC repeat expansion in the NOP56 gene causing SCA36.

In this issue of Neurology®, Ikeda et al. provide the first detailed phenotypic data firmly establishing that a combination of cerebellar ataxia and lower motor neuron disease are core clinical features of SCA36. However, there are some atypical features of the lower motor neuron phenotype; most patients had retained normal or increased tendon reflexes. In the presence of the lower motor neuron disease, hypertonia may imply the coexistence of the upper motor neuron disease. Although there is no other clinical evidence of upper motor neuron involvement, neurophysiologic assessment of the corticospinal tract and closer examination of the motor neurons in the motor cortex in brain autopsies would be of interest.

MRI of SCA36 brains showed cerebellar atrophy with some atrophy of the pons and middle cerebellar peduncle. The autopsy of a severely affected patient showed cerebellar atrophy with relatively preserved brainstem and prominent frontal cerebral atrophy. The frontal atrophy and dementia with no detectable β-amyloid plaques or vascular lesions in this patient raises the possibility that frontal lobe dementia is a part of the SCA36 phenotype in severely affected patients. A recent study showed that patients with SCA36 have a decrease in their frontal executive functions, which was related to the disease duration and the severity of ataxia. These changes were accompanied by a decline in frontal cerebral blood flow on SPECT. Unlike the GGGGCC expansion in ALS-FTD, the SCA36 GGCCTG does not appear to cause TDP43-positive inclusions. However, these 2 different hexanucleotide repeat expansions clearly target frontal lobe and motor neurons.

Overlap in clinical phenotypes and pathogenic mechanisms are frequently observed in expansion disorders. For example, expansions of polyglutamine-coding CAG repeats often cause SCA phenotypes and relatively short CGG expansions in the FMR1 gene also cause fragile X tremor-ataxia syndrome (FXTAS). Furthermore, short SCA2 expansions are associated with sporadic ALS, and SCA2 can present with clinical features of...
ALS. Therefore, whether these diseases, including SCA36 and the ALS-FTD, share common pathogenic mechanisms will be an interesting question to explore. The phenotypic expression of expansion diseases depends in part on the tissue-specific expression of the repeat-containing genes. The expression of NOP56 in Purkinje cells and lower motor neurons in the anterior horn and hypoglossal nucleus is consistent with the main phenotypes of cerebellar ataxia and lower motor neuron disease in SCA36. It should be noted that the tissue-specific expression pattern of (and also tissue-specific vulnerability to) expanded repeats may be sufficiently different to restrict phenotypic overlap.

Most, but not all, disorders with trinucleotide repeat expansions exhibit anticipation, or the occurrence of symptoms earlier in life with successive generations, likely due to progressively larger alleles in successive generations. Anticipation in DM2 families is not molecularly verifiable due to striking age-dependent instability of the CCUG tetranucleotide repeat expansion in blood DNA. Modest anticipation has been found in families with SCA10 and SCA31, which are caused by ATTCT and TGGAA pentanucleotide repeats. The lack of anticipation in SCA36 families is not totally surprising, however, since the mutant GGCCTG repeat in SCA36 shows neither an intergenerational expansion bias nor an inverse correlation between the age at onset and the repeat size. 

To date, SCA36 has been found exclusively in a small region of Japan on a founder haplotype. An important question is whether SCA36 cases exist outside Japan. Extensive screening of patients with ataxia of unknown type would provide the answer. Meanwhile, a scientific quest to understand the pathomechanism of SCA36 and other expansion diseases must continue as these genetic disorders are likely to provide important clues for their sporadic counterparts.

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REFERENCES